REMARKS

Restriction

The Office has required a restriction pursuant to 35 U.S.C. §121. The following three inventions have been identified:

Group I: Claims 1-17 (in part), 18, 19-24 (in part), 25, 26-32 (in part), 33, 34-39 (in part), 40, 41-46 (in part), 47, 48-53 (in part) and 54-123, drawn to compounds of Formula I, wherein A is nitrogen, pyrazolopyridines, compositions and method of treatments thereof, classified in call 544, subclass 262, 230, 106 and class 514, subclass 262.1 and 234.2.

Group II: Claims 1-17 (in part), 19-24 (in part), 26-32 (in part), 34-39 (in part), 41-46 (in part) and 48-53 (in part), drawn to compounds of Formula I wherein A is carbon, pyrazolopyrimidines, compositions and method of treatments thereof, classified in call 546, subclass 119 and 15, class 544, subclass 106 and class 514, subclass 303, 278 and 234.2.

Group III: Claim 123 (in part) drawn to a compound of Formula 2e, 1H-pyrazoles, classified in class 548, subclass 364.1 and 271.4

Applicants elect group I without traverse. The election is without prejudice to Applicants' right to file divisional applications directed to the subject matter not contained therein.

Please note that when A is N, the compound of Formula I is a pyrazolopyridimide and when A is carbon the compound is a pyrazolopyridine. Therefore Group I is directed to pyrazolopyrimidines. It is assumed that the error was typographical in nature.

To comply with Requirement for Restriction, Claims 1, 10, 17, 53, 55 and 123 have been amended.

With respect to the requirement for restriction between Groups II and III, Applicants elect to follow the procedure set forth in MPEP 821.04 and "Guidance on Treatment of Prodject and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. §103(b)", 1184 Off. Gazette 86 (1996), which permits rejoinder of method claims upon the allowance of a claim to the composition of matter.

Specification

The title of the invention is not believed to be descriptive. Applicants find the title Pyrazolo[4,3-d]pyrimidines as Cannabinoid Receptor Ligands and uses thereof to be acceptable.

Status of the Claims

Claims 1-123 are pending.

Claims 1-95, 99, 100, 105, 106, 110-112, 117, 118 and 123 have been amended.

Claims 104 and 116 have been canceled.

Rejection pursuant to 35 USC § 112, second paragraph

Claims 99-122 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regards as the invention. The Examiner asserts that it is unclear what diseases and treatments Applicants are intending to encompass.

The therapeutic use of cannabinoid receptor antagonists is well know to those skilled in the art. There are forty literature references cited in the IDS pertaining to their therapeutic values. Scientists have been studying cannabinoid receptor antagonists for many years. Their therapeutic roles as appetite suppressants, antipsychotics, in the treatments of memory/cognitive disorders, neuron-inflammatory pathologies and smoking cessation are described in *Expert. Opin. Ther. Patents (2002) 12(10):1475-1489.* cannabinoid receptor antagonists have been studied in clinical trials for the treatments of obesity, neuron-inflammatory pathologies and smoking cessation. (*See id.*) Reduction of 1-Dopa-induced dyskinesia in patients with Parkinson's disease, the management of acute schizophrenia and the amelioration of cognitive/memory dysfunctions associated with disorders such as Alzheimer's disease is described in *Prostaglandins, Leukotrienes and Essential Fatty Acids (2002) 66(2&3).101-121*. The use of cannibinoid antagonists in the treatment of disorders that have a prominent craving component, such as drug abuse, alcohol abuse and nicotine abuse is described in *Annu. Rev. Pharmacol. Toxicol. 2006. 46:101-22.* Without acquiescing to the propriety of this rejection, Claims 99, 106, 111 and 118 have been amended to include a list of disorders in order to facilitate the prosecution of this application. It is believed that the Claims as amended overcome the present rejection.

Claims 99-123 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regards as the invention. The Examiner asserts that the specification does not set forth any steps involved in determining how to identify "an animal in need of such treatment." The Examiners also asserts that it is unclear what diseases and treatments are intended to encompass.

As stated above, one skilled in the art is familiar with the therapeutic use of cannabinoid receptor antagonists. In addition one skilled in the art would be familiar with the risk factors and symptoms associated with such disorders. Based on the presence of such risk factors and symptoms, a physician can readily determine an animal in need of such treatment. It is believed that the Claim amendments described above overcome the present rejection.

Claims 98, 103, 109, 115 and 120 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regards as the invention. The Examiner asserts that the terms "analog" and "analog thereof" are indefinite. Ananlogs of Leptin and dehydroepiandrosterone (DHEA) are well known to those skilled in the art. Examples of Leptin analogs include LY355101 and LY396623 (Eli Lily & Co.). Examples of DHEA analogs include 16α-fluoro-5-androsten-17-one (fluaterone) and immunor (IM28). Applicants respectfully request withdrawal of this rejection.

Claims 1, 2, 4-6, 11, 19, 21, 34-36, 55, 57, 58-60, 63, 69 71, 80 and 82 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regards as the invention. The Examiner asserts that the term "acyl" is vague. The Applicants would like to draw the examiner's attention to page 31, line 30 – page 32, line 13 of the specification where the term "acyl" is defined. Specific examples are included. Applicants respectfully request withdrawal of this rejection.

Claims 107-110 and 118-122 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regards as the invention. The Examiner asserts that the term "pharmaceutical agent" is vague. The Applicants would like to draw the Examiner's attention to page 26, lines 7-12, page 27, lines 3-21, page 50, line3-26 and pages 51, line 30 – page 52, line 10 of the specification where specific examples of "pharmaceutical agents" are listed. Applicants respectfully request withdrawal of this rejection.

Rejection pursuant to 35 USC § 112, first paragraph

Claims 99-122 are rejected under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner assert that the Claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner asserts that the claimed invention is not enabled so that any person skilled in the art can make or use the invention without undue experimentation.

The test of enablement is a determination of whether the disclosure, when filed, contains sufficient information regarding the subject matter of the claims as to enable one skilled in the art to make or use the claimed invention. *Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916).* Even though the statute does not recite the term "undue experimentation" the Courts have interpreted to require that the claimed invention be enabled so that any person skilled in the art can make or use the invention without undue experimentation. *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

At the time of the effective filing date, April 23, 2003, it was known to those skilled in the art (see literature cited above and references cited in the IDS) to use cannabinoid receptor antagonists for the treatment of several disorders. Applicants assert that the disclosure enables any person skilled in the art to make or use the invention without undue experimentation for the following reasons.

Undue Breadth:

The Examiner in In re Vaeck, 20 USOQ2d 1438 stated the following:

> MPEP 796.03(z), "Undue Breadth," provides in part: n applications directed to intentions in arts were the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol,* 1938 C.D. 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield,* 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other

> appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...

The present specification discloses approximately 200 compounds and the methods of preparing such compounds. It is believed that the enumeration of approximately 200 species is sufficient to enable the scope of the Claims.

The Claims have been amended to include specific disorders. The Claims as amended overcome the rejection based on the scope of the diseases covered.

Nature of Invention and predictability in the art, Direction or Guidance, State of the prior art and working examples:

The §112 rejection in *In re Fisher* was based on an "open-ended" recitation in the claims where the potency recitation was "at least 1 International Unit of ACTH per milligram.

The Court stated:

> That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).*

In the present application there are numerous examples that have been shown to be cannabinoid receptor antagonists. Page 115, lines 9-15 of the specification describes a summary of the biological activity. All of the compounds were tested in the CB-1 receptor binding assay below. The compounds provided a range of binding activities from 0.2 nM to 1.6 μM. The compounds having an activity <20 nM were then tested in the CB-1 GTPγ [^{35}S] Binding Assay and the CB-2 binding assay described below in the Biological Binding Assays section. Selected compounds were then tested *in vivo* using one or more of the functional assays described in the Biological Functional Assays section. The scope of the Claims is enabled based on the showing of cannabinoid receptor antagonist activity and

what is known in the art regarding the therapeutic uses of cannabinois receptor antagonists.

The courts have made it clear that assertion in the in vitro and in vivo demonstration of therapeutic or pharmacological utility can be sufficient to support the claimed compounds. See *Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980) and Cross v. Iizuka, 753 F.2d 1040, 1046, 224 USPQ 739, 744 (Fed. Cir 1985).* The Federal circuit in *In re Wands* found that only 3 working examples out of 9 examples were sufficient for enablement. The Court reasoned that in view of the routine nature of the experimentation required and the high level of skill in the art, the evidence, was adequate to enable the full scope of the claims. *In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).* In the present application approximately 200 compounds were made, tested and demonstrated CB-1 receptor binding activity.

Skill in the Art:

According to the DSM-IV, Bulimia Nervosa is characterized by repeated episodes of binge eating followed by inappropriate compensatory behaviors such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise. The cannabinoids receptors in the brain are particularly located in the reward- or reinforcement-determining areas of the brain. Cannabinoid receptor antagonists attenuate the rewarding properties of opiods. To the extent that individuals binge-eat and purge for rewarding purposes, one would expect that a cannabinoid receptor antagonist would be useful in the treatment of Bulimia.

The Examiner asserts that "obesity, a condition which is just the opposite of bulimia nervosa, is not treated with the same pharmacotherapy as bulimia nervosa." Simple obesity is included in the *International Classification of Diseases* (ICD) as a general medical condition but does not appear in DSM-IV because it has not been established that it is consistently associated with a psychological or behavioral syndrome. It is not the opposite of Bulimia Nervousa. It is possible to treat both obesity and Bulimia Nervousa with the same pharmacotherapy because both can be treated with a drug such as antidepressants.

The uses of cannabinoid receptor antagonist in the treatment of cognitive/memory disorders associated with disorders such as Alzheimer's disease, the reduction of 1-Dopa-induced dyskinesia in patients with Parkinson's disease, inflammatory diseases and

gastrointestinal disorders are all know in the art. (See references cited above and in the IDS).

Many diseases and disorders can be treated generally with one drug. For example antidepressants are known to treat not only depression but also, for example, anxiety, sleep disorders, chronic pain, OCD, IBS, PMS, social phobia, obesity, eating disorders and smoking cessation. Anticonvulsants are known to not only treat seizure disorders but also, for example, diabetes mellitus, depression, schizophrenia, pain and bipolar disorder. The drug Chloroquine is an anti-malarial drug that is also known to treat rheumatoid arthritis and other inflammatory diseases. Just because different diseases and disorders occur at different locations and by different modes of action in the body does not mean that they can not be treated with one drug. One drug could hit many different targets and pathways so it is possible for one drug to treat different disorders and diseases that are not related. In addition many unrelated diseases and disorders are mediated by the same targets.

Treatment of diseases and disorders include the treatment of the symptoms. While there is no known cure for Parkinson's disease cannabinoid receptor antagonists are known to treat Dyskinesia. And while PID would be treated with antibiotic and appendicitis would be treated with surgery both would be treated with an anti-inflammatory and/or a pain killer.

The Claims cover many different disorders all of which are believed to benefit from the treatment of a cannabinoid receptor antagonist. This is well documented in the literature. Based on what is known in the art and what is disclosed in the specification the Applicants are certain that the present Claims are enabled.

Claims 1-123 are rejected under 35 USC § 112, first paragraph, because the specification does not reasonably provide enablement for solvates or hydrates. The Claims have been amended to remove the terms "solvates" and "hydrates." Applicants respectfully request withdrawal of this rejection.

Conclusion

Claims 1-95, 99, 100, 105, 106, 110-112, 117, 118 and 123 have been amended. It is believed that the Claims are in condition for allowance, and it is respectfully requested that the application be passed to issue.

If the Examiner believes a telephonic interview with Applicants' representative would aid in the prosecution of this application, she is cordially invited to contact Applicants' representative at the below listed number.

Respectfully submitted,

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